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(54) MOULDED PHARMACEUTICAL COMPOSITIONS

(71) We, MERCK PATENT GESELLSCHAFT MIT BESCHRANKTER HAFTUNG, a German corporate body of 61 Darmstadt, Frankfurter Strasse 250, Germany, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement: —

This invention is concerned with moulded pharmaceutical compositions from which, on administration, there is delayed release of active material.

Galactomannans (hereinafter referred to, for brevity, as GM) are natural hydrocolloids found, for example, in the seeds of guar pods (*Cyamopsis tetragonoloba*) and in the seeds of carob tree pods (*Ceratonia siliqua*). Chemically they are polysaccharides having an elongated main chain of mannose units with single-membered galactose units branching therefrom. In the GM obtained from guar endosperm flour, there is a statistical average of one galactose unit side chain for every two mannose units, whilst in GM obtained from carob tree seed flour, there is one galactose unit side chain for every four mannose units. GM are soluble in water, heating sometimes being necessary. Even low concentrations of GM can give high viscosity colloidal solutions.

The use of GM for the production of durable water-soluble vitamin compositions is known. It is also known to use GM in quantities of up to 10% by weight as an adjuvant in the production of tablets.

Neither the known GM-containing vitamin compositions nor the known GM-containing tablets have any appreciable delayed release of active material. The use of GM for the preparation of pharmaceutical mouldings from which the release of the active material is delayed, is novel.

We have found that if more than 20% by weight of GM is used in the production of pharmaceutical mouldings, rapid disintegration of the latter is prevented by hydration of the surface of the GM so that the active material must diffuse through this jelly-like hydrate coating, and, as a result, there is delayed release of the active material from such mouldings, this being a property which is desired in a number of pharmaceutical compositions.

According to the present invention, therefore, we provide a pharmaceutical moulding from which there is delayed release of active material, characterised in that the moulding contains at least 20% by weight of galactomannan.

The present invention also comprises a process for the preparation of pharmaceutical mouldings from which there is delayed release of active material, which comprises pressing a mixture comprising at least 20% by weight of galactomannan and at least one pharmaceutically active material.

It is known to prepare delayed-release pharmaceutical mouldings by providing such mouldings with a water-insoluble plastics matrix from which the active material is released only slowly. In comparison with these, the mouldings according to the invention have the advantage of being very simple to prepare and also the advantage that GM are completely physiologically inert and are toxicologically acceptable.

The term "moulding" is used in this specification to refer to all solid formulations which are produced by pressing under pressure, in particular tablets and dragee cores. Mouldings having the required delayed release properties are obtained only by the use of pressure. The known GM-containing compositions made without the application of pressure, have this property only to a negligible degree, if at all. The term "moulding" is to be understood to include all the various geometric shapes which can be moulded using appropriate tabletting machines, the most usual shapes being cylinders, spheres, hemispheres and combinations thereof, the shape being, of course, determined by the dies used in the tabletting machine. The diameter of the mouldings is generally in the range of from 3 to 30 mm, more particularly 5 to

20 mm and the thickness is usually from 1 to 10 mm, preferably 2 to 7 mm.

The mouldings according to the invention contain one or more active materials. Multi-vitamin-mineral salt compositions may, for example, contain up to thirty active materials. Apart from the usual criteria of state of aggregation and stability, the choice of suitable active materials is not subject to any limitations. More particularly, water-soluble and/or water-insoluble or difficultly water-soluble active materials may be used. Suitable active materials include, for example, vitamins, such as vitamin A and its esters; vitamin B_1 (thiamine) and its derivatives, for example thiamine mononitrate and thiamine phosphates; vitamin B_2 (lactoflavin, riboflavin); vitamin B_6 (pyridoxin) and its derivatives, for example the hydrochloride or the phosphate, pyridoxal, pyridoxal phosphate, pyridoxamine, pyrithioxine; vitamin B_{12} and its derivatives, for example hydroxo-cobalamin; vitamin C (ascorbic acid) and its derivatives, for example calcium ascorbate or ascorbyl palmitate; vitamin D_2 and D_3 and their derivatives; vitamin E and its derivatives, for example α-tocopheryl acetate; vitamin K, for example Menadione; biotin; pantothenic acid and its derivatives, for example calcium-D-pantothenate; rutin; nicotinic acid amide; antibiotics, such as penicillin and its derivatives, for example phenoxymethyl penicillin, phenoxyethyl penicillin, and ampicillin; tetracyclines, such as chloro- or hydroxy-tetracyline; chloramphenicol; steroids, such as corticoids, for example hydrocortisone, cortisone, prednisolone, prednisone, prednylidene, fluprednylidene, dexamethasone, betamethasone; or progresterone and its derivatives, for example chlormadinone acetate; testosterone and nortestosterone and their derivatives, for example 17α-methyltestosterone, tiomesterone or norethisterone; estrogens, for example estrone or estradiol and their esters; cardioactive glycosides; for example digitoxin, lanatoside C or peruvoside; enzymes, for example pancreatin or bromelin; alkaloids, for example ergocristine, ergonovine, morphine, papaverine or scopolamine; other pharmaceuticals of all kinds, for example acetylsalicylic acid, amphetamine, barbituric acid and derivatives thereof, for example barbital, cyclobarbital or phenobarbital and salts thereof, carbachol, carisoprodol, chlorodiazepoxide, chlorothiazide, diazepam, dihydro-hydroxycodeinone and its salts, eupaverine, fencamfamine, hydrochlorothiazide, 7 - (2 - hydroxypropyl) - theophylline, isopropylantipyrine, meprobamate, methaqualone, parabromodylamine, phenacetin, piperazine adipate, 3-pyridine methanol and its salts, racephedrine and its salts, sulphanilamide and its derivatives, for example, sulphaperine or 2 - sulphanilamido - 5 - ethyl - pyrimidine, *l*, or *d*-thyroxine, trichloromethiazide or *l*- or *d*-triiodothyronine.

The active material content of the mouldings may be varied within wide limits. Its lower limit is the minimum active dose, and the upper limit is determined by the minimum GM content which still has a delaying action on the release of the active material. The active material content may, therefore, be from about 0.01 to 80% by weight.

Any of the commercially available GM's may be used in the mouldings according to the invention. Two commercial products having mean molecular weights of about 50,000 and about 280,000, respectively, have, for example, proved suitable. The higher molecular weight GM has a greater retarding effect than the lower molecular weight material. GM having a mean molecular weight of from about 30,000 to about 400,000, and preferably from about 40,000 to about 350,000, are, in principle, suitable for use in the mouldings according to the invention. The GM content of the mouldings may be from 20 to 99.99, preferably from 20 to 90%, by weight. Measurable retardation of active material release also occurs at lower GM contents, but these are usually unsatisfactory for practical purposes. In practice, the GM's used will normally be those which form high viscosity solutions in low concentrations and hence have a high dilution effect.

The mouldings according to the invention may be prepared without the addition of other adjuvants, in which case they contain no constituents other than the active material and the GM. However, it is usually preferred that they should contain one or more pharmaceutical adjuvants. Conventional extenders and fillers, swelling agents, adsorption agents, moisturising agents, binders, lubricants, disintegrating agents and anti-disintegrating agents may, for example, be present, for example carbohydrates, such as starch (for example wheat starch, rice starch, cornstarch, and potato starch), sugar (for example lactose and saccharose), dextrin, inulin, cellulose and its derivatives (for example cellulose powder, microcrystalline cellulose, carboxymethylcellulose and its salts, for example the sodium salt, methyl cellulose, ethyl cellulose, hydroxy ethyl cellulose, and hydroxypropylcellulose); alginic acids and their salts, agar-agar, tragacanth, gum arabic, pectins (for example dried apple pectin or sodium amylopectin glycolate); shellac; higher alcohols, such as stearyl alcohol, cetyl alcohol; hexitols, such as mannitol or sorbitol; carboxylic acids, such as benzoic acid, citric acid, stearic acid, palmitic acid, and stearin; fats, such as cocoa butter; salts and soaps such as calcium lactate, calcium or magnesium stearate, sodium lauryl sulphate; defatted skim milk powder, urea; gelatine; casein, chloresterol, polyethylene glycols and their esters, for example with fatty acids; polyvinyl compounds, such as polyvinyl pyrrolidone, polyvinyl alcohol, poly-

vinyl acetate, vinyl pyrrolidone/vinyl alcohol or vinyl alcohol/vinyl acetate copolymers; paraffin; inorganic additives, such as silica (more particularly finely divided silica), aluminium oxide, aluminium hydrosilicate, aluminium hydroxide, calcium carbonate, calcium phosphate, sodium chloride, sodium bicarbonate, and talc. Some of these additives contribute to increasing the retardation effect, for example polyvinyl compounds and cellulose derivatives.

Conventional preservatives, stabilisers or wetting agents, emulsifiers, salts for controlling osmotic pressure, buffer substances, colorants, flavours and/or aromatic substances may also be included.

The mouldings according to the invention may be pressed in the conventional manner, the constituents being pre-mixed, ground and sieved and granulated if required. Pressing without pre-granulation is preferred (direct pressing, powder pressing) at pressures of from 1,000 to 10,000 kp/cm². Any conventional tabletting machines may be used for pressing the mouldings, rotary machines having agitator chamber filler shoes being preferred.

In the case of difficultly flowing powder mixtures, it is advantageous to use additional agitating, shaking or vibrating devices. It is also possible to incorporate the active material as an embedded or encapsulated material which has been produced, for example, by spray drying.

The mouldings obtained may, if desired, be coated (for example with a dragee coating or a film of varnish). These coatings may, if desired, exert an additional effect on the digestion of the moulding or the liberation of the active material. In addition, the coating, particularly dragee coatings, may contain medicaments which are liberated after administration without any delay. Mouldings which ensure immediate liberation of one or more active materials in addition to the delayed release of one or more other active materials may be produced, for example, in the form of dry coated tablets or multi-layer tablets. In dry coated tablets, the core must contain the GM-containing combination, while the coating layer consists of a normal active material and adjuvant combination. A similar procedure is adopted for the production of multi-layer tablets, that is one of the layers must contain at least 20% by weight of GM.

The delayed release of the active material from the mouldings according to the invention can be determined, for example, in a "USP method" digester. A suitable digester is made, for example, by Messrs. Erweka, Heusenstamm bei Hanau, Germany. Incubation is, for example, usually carried out at 37°C with:

1. water
2. synthetic gastric juice (pH 1.2; according to USP XVIII)
3. synthetic intestinal juice (pH 7.5; according to USP XVIII) or
4. by Munzel's half-change method, starting with synthetic gastric juice, half the incubation liquid being removed and replaced by synthetic intestinal juice after every hour.

As a rule, under these conditions, 50% ("50% values") of the active material present is released (liberated) from the mouldings according to the invention within 1 to 2 hours, and 90% in 7 to 10 hours. The higher the proportion of GM in the moulding, the greater the retardation of the release of the active material; for example, the "50% value" of ascorbic acid tablets can be raised from 1 hour to 2 hours by raising the GM content from 21 to 35% by weight.

The principle of the retarded liberation of the active material from a GM-containing moulding is based on the hydration of the colloid in the presence of water or gastric or intestinal juice. Swelling occurs under these conditions and progresses slowly from the surface as the moisture penetrates the moulding. A permeable jelly-like coating is formed in this way. Liberation of the active material does not, therefore, depend upon the pH and is, in principle, largely independent of the enzymatic conditions of the digestive juices which may, of course, be disturbed in the sick.

The following examples give formulations for mixtures which can be pressed according to the invention to form tablets or dragee cores without prior granulation, so that each of the resulting mouldings has the indicated composition. If dragees are required, the cores are then conventionally treated with a sugar-coating suspension. Coating the cores with a layer of varnish gives varnished tablets. Various types of GM were used, the average molecular weights being indicated in brackets. D=diameter, St=thickness of moulding. These examples are given by way of illustration only:—

Example 1

250 mg	of l-ascorbic acid
350 mg	GM (50,000)
90 mg	cellulose powder
50 mg	cornstarch
20 mg	finely divided silica
10 mg	magnesium stearate

D=13 mm, St=4.6 mm

Example 2

250 mg	of l-ascorbic acid
250 mg	GM (50,000) or GM (280,000)
100 mg	lactose

40 mg cellulose powder
30 mg wheat starch
20 mg finely divided silica
10 mg calcium stearate

D=12 mm, St=5 mm; the "50% values" (=liberation of 50% of ascorbic acid contained in the tablet, in the Erweka-digester) with water at 37°C were 2 hours using the lower molecular weight GM and 2¾ hours using the higher molecular weight GM; the entire active substance content of tablets which did not contain any GM was completely dissolved in the solvent after just half an hour.

Example 3

250 mg of l-ascorbic acid
150 mg GM (50,000)
190 mg lactose
40 mg carboxymethylcellulose, Na salt
35 mg rice starch
25 mg finely divided silica
10 mg magnesium stearate

D=12 mm, St=5 mm; "50% value" (Half Change Method): 1 hour.

Example 4

375 mg of pyridyl - 3 - carbinol - tartrate
450 mg GM (280,000)
90 mg cellulose powder
63 mg potato starch
30 mg finely divided silica
10 mg magnesium stearate

D=15 mm, St=7 mm; 50% value (synthetic gastric juice); 2 hours.

Example 5

10 mg of pyridoxol hydrochloride
40 mg GM (280,000)
25 mg lactose
10 mg cellulose powder
10 mg corn starch
3 mg finely divided silica
2 mg calcium arachinate

D=7 mm, St=2 mm.

Example 6

10 mg Mepiprazol dihydrochloride
64 mg GM (280,000)
72 mg calcium phosphate
8 mg cellulose powder
4 mg finely divided silica
2 mg magnesium stearate

D=8 mm, very curved shape; 50% value (in synthetic gastric juice): 1 hour.

Example 7

2 mg hydrocortisone
65 mg GM (280,000)
43 mg lactose
20 mg cellulose powder
15 mg wheat starch
10 mg finely divided silica
5 mg magnesium stearate

D=8 mm, very curved shape; 50% value (half-change method): 2 hours.

Example 8

100 mg l-ascorbic acid
100 mg GM (280,000)
100 mg lactose
20 mg methylcellulose
15 mg rice starch
10 mg finely divided silica
5 mg magnesium stearate

D=10 mm, St=3.4 mm.

Example 9

250 mg l-ascorbic acid
350 mg GM (280,000)
50 mg potato starch
20 mg finely divided silica
10 mg magnesium stearate

D=13 mm, St=4 mm.

Example 10

250 mg ascorbic acid
350 mg GM (280,000)
90 mg cellulose powder
50 mg potato starch
10 mg magnesium stearate

D=13 mm, St=4.5 mm.

Example 11

250 mg ascorbic acid
350 mg GM (280,000)
60 mg talc

D=13 mm, St=3.8 mm

Example 12

10 mg of 1% vitamin B_{12} concentrate formed by spraying (containing 0.1 mg vitamin B_{12} and 9.9 mg lactose)

400 mg GM (280,000)
24.25 mg cellulose powder
9 mg finely divided silica
6.75 mg magnesium stearate

D=11 mm, St=4.1 mm

Example 13

10 mg of a triturated mixture consisting of 0.1 mg of vitamin B_{12} (cyanocobalamin) and 9.9 mg of lactose

100 mg GM (280,000)
299.25 mg of lactose
25 mg of cellulose powder
9 mg of finely divided silica
6.75 mg magnesium stearate

D=11 mm, St=3.5 mm.

Example 14

585 mg phenobarbital
150 mg GM (280,000)
7.5 mg finely divided silica
7.5 mg magnesium stearate

D=13 mm, St=4 mm.

Example 15

525 mg acetylsalicylic acid
180 mg GM (280,000)
7.5 finely divided silica
37.5 talc

D=13 mm, St=4.4 mm.

Example 16

A powder mixture was granulated and then pressed into tablets of the following composition:

585 mg acetylsalicylic acid
150 mg GM (280,000)
7.5 mg finely divided silica
7.5 mg magnesium stearate

D=13 mm, St=4.5 mm.

Example 17

Tablets of the following composition were pressed on a hand press from a 0.1% dispersion of vitamin B_{12} (cyanocobalamin) in GM (50,000):

0.1 mg vitamin B_{12}
99.9 mg GM (50,000)

D=7 mm, St=2 mm

Example 18 (Two-layer tablets

Powder mixtures were sieved and mixed and after suitable granulation were pressed on a two-layer tabletting machine to form two-layer tablets of the following composition:

a) "Retard coating" giving a delayed release of the active material:

12 mg 50% dispersion of panthenol is (formed by spraying),
GM (50,000), (formed by spraying),
2 mg pyridoxolium chloride
55 mg ascorbic acid
15 mg nicotinic acid amide
220 mg GM (280,000), granulated
141 mg lactose, granulated
5 mg cellulose powder
50 mg talc

b) "Normal layer" with normal release of active material:

4.4 mg vitamin A acetate
3.3 mg 33.3% dispersion of vitamin B_1 in methyl cellulose (formed by spraying),
1.65 mg riboflavin
1.3 mg 0.1% dispersion of vitamin B_{12} in GM (50,000), (formed by spraying),
4 mg 50% mixture of vitamin E acetate and finely divided silica,
163.35 mg lactose, granulated
2 mg cellulose powder
20 mg talc

D=13 mm.

WHAT WE CLAIM IS:—

1. A pharmaceutical moulding from which there is delayed release of active material, characterised in that the moulding contains at least 20% by weight of galactomannan.

2. A process for the preparation of pharmaceutical mouldings from which there is delayed release of active material, which comprises pressing a mixture comprising at least 20% by weight of galactomannan and at least one pharmaceutically active material.

3. A pharmaceutical moulding substantially as herein described in any of the Examples.

4. A process for the preparation of pharmaceutical mouldings substantially as herein described in any of the Examples.

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